Non-coding RNAs derived from an alternatively spliced REST transcript (REST-003) regulate breast cancer invasiveness.

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Public Summary:
Silencing Transcription factor (REST) has a well-established role in regulating transcription of genes important for neuronal development. Its role in cancer, though significant, is less well understood. We show that REST downregulation in weakly invasive MCF-7 breast cancer cells converts them to a more invasive phenotype, while REST overexpression in highly invasive MDA-MB-231 cells suppresses invasiveness. Surprisingly, the mechanism responsible for these phenotypic changes does not depend directly on the transcriptional function of REST protein. Instead, it is driven by previously unstudied mid-size (30-200 nt) non-coding RNAs (ncRNAs) derived from the first exon of an alternatively spliced REST transcript: REST-003. We show that processing of REST-003 into ncRNAs is controlled by an uncharacterized serine/arginine repeat-related protein, SRRM3. SRRM3 expression may be under REST-mediated transcriptional control, as it increases following REST downregulation. The SRRM3-dependent regulation of REST-003 processing into ncRNAs has many similarities to recently described promoter-associated small RNA-like processes. Targeting ncRNAs that control invasiveness could lead to new therapeutic approaches to limit breast cancer metastasis.

Scientific Abstract:
RE1-Silencing Transcription factor (REST) has a well-established role in regulating transcription of genes important for neuronal development. Its role in cancer, though significant, is less well understood. We show that REST downregulation in weakly invasive MCF-7 breast cancer cells converts them to a more invasive phenotype, while REST overexpression in highly invasive MDA-MB-231 cells suppresses invasiveness. Surprisingly, the mechanism responsible for these phenotypic changes does not depend directly on the transcriptional function of REST protein. Instead, it is driven by previously unstudied mid-size (30-200 nt) non-coding RNAs (ncRNAs) derived from the first exon of an alternatively spliced REST transcript: REST-003. We show that processing of REST-003 into ncRNAs is controlled by an uncharacterized serine/arginine repeat-related protein, SRRM3. SRRM3 expression may be under REST-mediated transcriptional control, as it increases following REST downregulation. The SRRM3-dependent regulation of REST-003 processing into ncRNAs has many similarities to recently described promoter-associated small RNA-like processes. Targeting ncRNAs that control invasiveness could lead to new therapeutic approaches to limit breast cancer metastasis.